PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	09.07.2003
Applicant's or agent's file reference: P1014PC00	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK02/00547	20.08.2002	20.08.2001

International Patent Classification (IPC) or both national classification and IPC
A61K39/00

Applicant
PHARMEXA A/S et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20.12.2003

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-99 as originally filed

Claims, Numbers

1-38 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

Sequence listing part of the description, pages:

1-10, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this opinion.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-24,36

   because:

   ☒ the said international application, or the said claims Nos. 1-24,36 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-15,18-38
Inventive step (IS)	Claims	1-38
Industrial applicability (IA)	Claims	

2. Citations and explanations

   see separate sheet

Reference is made to the following documents:

D1: WO 00 72880 A (SCHENK DALE B ;YEDNOCK TED (US); BARD FREDERIQUE (US); NEURALAB LT) 7 December 2000 (2000-12-07)

D2: WO 01 42306 A (CHAIN BENJAMIN ;MINDSET BIOPHARMACEUTICALS USA (US)) 14 June 2001 (2001-06-14)

D3: WO 99 27944 A (SCHENK DALE B ;ATHENA NEUROSCIENCES INC (US)) 10 June 1999 (1999-06-10) cited in the application

D4: WO 01 62284 A (NIELSEN KLAUS GREGORIUS ;BIRK PETER (DK); JENSEN MARTIN ROLAND (DK) 30 August 2001 (2001-08-30) cited in the application

D5: LEES A ET AL: 'Enhanced immunogenicity of protein-dextran conjugates: I. rapid stimulation of enhanced antibody responses to poorly immunogenic molecules' VACCINE, BUTTERWORTH SCIENTIFIC. GUILDFORD, GB, vol. 12, no. 13, 1994, pages 1160-1166, XP002082853 ISSN: 0264-410X cited in the application

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-24,36 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

When the applicant reformulates the current method for treatment claims, he should chose the following form:

A second medical use claim acceptable by this authority would read:
The use of substance/compound X for the preparation of a medicament for the treatment of disease Y (EPO Guidelines C-IV 4.2-4.3).
Defining the disease state merely in terms of molecular mechanisms or protein/enzyme expression patterns is unclear (Art. 6 PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or

industrial applicability; citations and explanations supporting such statement

The International Search Report contains a document of the P category. Should the applicant envisage to enter the European phase, the subject matter of this document D4 may become pertinent concerning novelty and inventive step.

V.1 INVENTION

Auto-immunisation therapy of Alzheimer's disease with beta-amyloid (APP,A-beta) analogues (protein, nucleic acids or microorganisms expressing the latter) containing or linked to a foreign T-Helper epitope (can be a promiscous epitope such as P2 or P30 (from Tetanus toxoid), diphteria toxoid epitope, diphtheria toxoid epitope, influenza virus hemagglutinin epitope, P. falciparumn CS epitope) and optionally to a polyhydroxypolymer. Also claimed is a cell-line transformed with a vector incorporating the nucleic acid coding for the above agent.
The analogues are designed to break the auto-tolerance against APP or A-beta so that antibodies are raised against APP or A-beta, where the response is preferably directed against the intra-cellular parts of these peptides as to avoid an immune-response against cells expressing the peptides.
novel, but the P-doc entirely discloses them, so big problems in EP-phase.

V.2 CLARITY

The claims currently contain a plethora of formulations that merely state an underlying problem or a desirable function without indicating technical features that would solve the problem or deliver the function. This renders the corresponding claims unclear (Art. 6 PCT). To overcome this objection, the technical features have to be introduced into the claim.
All of the following formulations are objected to:

Claim 2
- 'substantial fraction of B-cell epitopes ... are preserved'
- 'one first moiety ... which effects targeting ... to an APC'
- 'one second moiety ... which stimulates the immune system'
- 'one third moiety ... which optimizes presentation of the analogue to the immune system'

Claim 5
- 'results in a substantial preservation of the overall tertiary structure'

Claims 10,11
- 'B-cell epitopes which are not exposed to the extracellular phase'
- 'analogue lacks at least one B-cell epitope which is exposed to the extracellular phase'

In claim 1, subsection a), is defined a subsequence of SEQ ID 2 through residues **672**- 714 and also through residues **673**-714. Clarification is needed.

Claim 14 refers back to claims 22 and 23, where it should probably read 12 and 13.

Claim 15 should read 'covalently **or** non-covalently' instead 'covalently **of** non- covalently'.

Claim 36 is dependent on claims 1 to 14 and should be renumbered, reflecting its dependency.

The applicant should delete all statements similar to 'incorporated herein by reference'.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1,D2 is not mentioned in the description, nor are these documents identified therein.

Although claims 1 and 24, 26 and 37, 33 and 38 (pairwise) have been drafted as separate independent claims, they appear to relate effectively to the same subject- matter and to differ from each other only with regard to the definition of the subject- matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of in- dependent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, claims 1 and 24, 26 and 37, 33 and 38 do not meet the requirements of Article 6 PCT.

In order to overcome this objection, it would appear appropriate to file an amended set of claims defining the relevant subject-matter in terms of a minimum number of claims in each category followed by dependent claims covering features which are merely op- tional (Rule 6.4 PCT).

V.3 PRIOR ART

If not otherwise specified, subject matter of cited documents relates to the passages indicated in the search report.

D1
Synthetic vaccines for the treatment of Alzheimer's comprising one or more (different) B cell epitopes of Abeta (Abeta 1-7 or 3-9, but also up to 20 aas) and one or more (different) promiscous (universal) T helper epitopes (e.g. tetanus or diphtheria toxoid). The fusion peptides can be arranged in all possible linear forms (specific examples given) or even dendritic forms (MAPs: two or more of the fusion peptides are linked separately to a peptidic backbone). The idea is to generate a B cell response against A beta without affecting APP.
The vaccines can be administered in peptide form, as nucleic acids or via viruses/bacteria, together with adjuvants, in a dose of > 10 ug peptides. The linear fusion peptides are produced through standard recombinant technology.

D2
Synthetic peptide vaccines comprising one or several (different) copies of a promiscous (or immunodominant) T helper epitope (e.g. tetanus or diphteria toxoid), a spacer of 0-5 aas (glycine) and a B cell epitope (2-5 aas) of naturally occuring cleavage peptides of beta-APP (e.g. of A beta 40/42/43 or fragments thereof), for the treatment of Alzheimer's disease. The idea is to break autotolerance and raise antibodies against A beta without generating an immune response compromising beta-APP's natural function. The vaccines can be produced by standard DNA/protein technology. The T helper epitope can be lipid-modified. Administration can incur adjuvants, one or multiple doses (unit of 0.5-1000 ug per kg weight), poly(lactide-co-glycolide) microparticles, by oral or parenteral route.
Additionally, a mixture of synthetic peptides with different T helper epitopes can be administered.

D3
A synthetic vaccine to treat Alzheimer's where Abeta 42 (or active fragments) is fused to peptides promoting the immune response against Abeta, e.g. tetanus or diphtheria toxoid. The Abeta part can be present in multiple copies. The fusion peptide can be administered with adjuvants at a dose of at least 1 or 10 ug, or in nucleic acid form, e.g. in a viral vector.

D5
Rapid stimulation of enhanced antibody responses to poorly immunogenic molecules by conjugating the epitope to a dextran.

V.4 NOVELTY

Remarks under Art. 33(2) PCT

Document D1 anticipates claims 1-15,18-38.
Document D2 anticipates claims 1-4,7-15,18-38.
Document D3 anticipates claims 1-9,15,18-32,36,37.

Claims 1-15,18-38 therefore appear to be not novel according to Art. 33(2) PCT.

V.5 INVENTIVE STEP

Remarks under Art. 33(3) PCT

Document D1, which is considered to represent the most relevant state of the art for claims 16 and 17, discloses a synthetic vaccine comprising a B cell epitope from A beta and a T helper epitope, where these epitopes are fused together and two or more of these fusion peptides can be linked separately to a peptidic backbone, from which the subject-matter of claims 16 and 17 differs in that a polyhydroxypolymer such as a polysaccharide is employed for the backbone.

The technical effect achieved is increasing the immunogenicity of the construct, where in the case of claims 16 and 17 the backbone itself promotes immunogenicity.

The problem to be solved by the present invention may therefore be regarded as how to further increase the immunogenicity of a synthetic peptide vaccine for AD.

The solution proposed in claims 16 and 17 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

In D5 from 1994 it was already shown that poorly immunogenic molecules can be enhanced in their immunogenicity by coupling them to a sugar, increasing the titre of antibodies raised against the epitopes.
It is not exaggerated to state the the person skilled in the art was generally aware of the possibility to link B cell epitopes to polysaccharide carriers as a standard tool to further enhance the B cell response.
Therefore, it appears obvious to combine a polysaccharide backbone as disclosed in D5 with the B and T epitopes of the present invention.